Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 27-46 are pending in the application. Claims 47-75 are sought to be canceled without prejudice to or disclaimer of the subject matter therein. Applicants retain the right to pursue the subject matter of the canceled claims in one or more continuing applications. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. The Interview of October 9, 2002

Applicants thank the Examiner for extending the courtesy of allowing Applicants' representatives to interview the Examiner, the Supervisory Examiner and the Patent Practice Specialist. Applicants have filed in the USPTO a "Statement Concerning the Substance of the Interview" on November 7, 2002.

II. Restriction Requirement

The Examiner has stated that claims 37-75 are "generic to a plurality of disclosed patentably distinct species of polypeptide fragment of SEQ ID NO:2." (Paper No. 23, page 2.) Based on this contention, the Examiner has requested that Applicants "elect a single disclosed species of peptide fragment, even though this requirement is traversed." (*Id.*)

Claims 47-75 have been canceled. Thus, of the claims in which the Examiner stated are "generic to a plurality of disclosed patentably distinct species," only claims 37-46 are pending. It is noted that claims 37-46 relate to amino acids 350 to 420 of SEQ ID NO:2. Specifically, claims 37-46 are directed to isolated proteins comprising 30 contiguous amino acids of a polypeptide having the amino acid sequence from 350 to 420 of SEQ ID NO:2 (claim 37); isolated proteins comprising 50 contiguous amino acids of a polypeptide having the amino acid sequence from 350 to 420 of SEQ ID NO:2 (claim 38); and isolated proteins comprising amino acid residues encoded by a first polynucleotide which hybridizes to a second polynucleotide consisting of nucleotides 1245 to 1457 of SEQ ID NO:1 (corresponding to amino acids 350 to 420 of SEQ ID NO:2), or the complement thereof under specified stringent conditions (claim 43). As such, claims 37-46 are directed to related subject matter.

Even assuming, *arguendo*, that there are subgenuses within claims 37-46 which represent distinct or independent subject matter, Applicants submit that to search and examine the subject matter of the subgenuses together would not be a serious burden on the Examiner. Applicants submit that there is significant overlap between the polypeptides of encompassed by the subgenuses as each subgenus relates to the same portion of SEQ ID NO:2. This significant overlap thereby makes it a simple matter for the Examiner to search and examine publications. The M.P.E.P. § 803, states:

> If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions.

Thus, even assuming, *arguendo*, that the "species" represented distinct or independent subject matter, restriction remains improper unless it can be shown that the search and examination of all groups would entail a "serious burden." M.P.E.P. § 803. In the present situation, no such showing has been made.

Further, Applicants point out that the Examiner has not addressed MPEP § 803.04, directed to nucleotide sequences. Pursuant to the notice *Examination of Patent Applications Containing Nucleotide Sequences*, 1192 O.G. 68 (November 19, 1996), §803.04 holds that even when nucleotide sequences encoding different proteins are contained in an application, a reasonable number, normally ten, sequences will be examined in a single application. Applicants submit that the instant amino acid sequences constitute related fragments of the same protein, rather than different proteins as contemplated by § 803.04. "[N]ucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together." (MPEP § 803.04.) Thus, Applicants respectfully submit that the present requirement for election is improper. However, even if the Examiner contends that the instant amino acid sequences constitute different proteins within the scope of §803.04, Applicants submit that a reasonable number of such sequences should be examined together, and the Examiner has given no indication why the search of seven sequences is unreasonable in the present case.

Thus, Applicants respectfully request that the Restriction Requirement be withdrawn so the subject matter of claims 37-46 be examined together.

III. Claim Objections

The Examiner has objected to claim 64 as allegedly reciting an improper Markush group. (Paper No. 23, page 3.) Solely to advance to prosecution and not in acquiescence to the Examiner's rejection, Applicants have canceled claim 64 without prejudice or disclaimer. Applicants retain the right to pursue the subject matter of claim 64 in one or more continuing applications.

Cancellation of claim 64 renders the Examiner's objection moot. Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

IV. Rejections under 35 U.S.C. § 101

The Examiner has maintained the rejection of claims 27-75 under 35 U.S.C. § 101 as allegedly not supported by either a credible, substantial and specific utility or a well established utility. (Paper No. 23, page 3.) Applicants respectfully traverse the Examiner's rejection.[1]

Initially, the Examiner is reminded that Applicants need only provide one credible assertion of specific and substantial utility for the claimed invention to satisfy the utility requirement. "When a properly claimed invention meets at least one stated objective, utility under 35 U.S.C. § 101 is clearly shown." *Raytheon v. Roper*, 724 F.2d 951, 958 (Fed. Cir. 1983). According to the MPEP, a "specific utility" is specific to the subject matter claimed and is to be contrasted with a general utility that would be applicable to the broad class of the invention. (MPEP § 2107.01(I).) A "substantial utility" defines a "real world" use. (*Id.*) The

---

[1] Applicants point out that claims 47-75 have been canceled without prejudice or disclaimer and that clams 27-46 are pending on entry of the present amendment. Accordingly, the present rejection will be addressed as it pertains to the pending claims.

MPEP states that "[a]n assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition . . . defines a 'real world' context of use. . . ." (*Id.*) A statement of utility is presumed to be credible unless the Examiner establishes that it is more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility. (MPEP § 2107.02(III).)

A. One of ordinary skill in the art would find it credible that the claimed invention has utility in diagnostic applications.

The specification discloses that the claimed nucleic acid molecules have utility in, among other things, diagnostic applications for detecting disease. More specifically, the specification discloses that:

> The present invention also provides diagnostic assays such as quantitative and diagnostic assays for detecting levels of DR3 or DR3-V1 protein. Thus, for instance, a diagnostic assay in accordance with the invention for detecting overexpression of DR3 or DR3-V1, or soluble form thereof, compared to normal control tissue samples may be used to detect the presence of tumors.

(Specification, page 5, lines 10-14.)

The present application is directed to nucleic acids encoding a novel member of the Tumor Necrosis Factor (TNF) family of receptors, specifically, a novel death domain-containing TNF receptor. (Specification at page 1, lines 10-16.) The instant specification discloses that polypeptides encoded by nucleic acids of the invention are expressed by "lymphocytes, fibroblasts, macrophages, synovial cells, activated T-cells, lymphoblasts and epithelial cells." (Specification at page 38, lines 5-8.) Furthermore, the instant specification discloses that nucleic acid molecules of the present invention are involved in "[d]iseases

associated with increased cell survival, or the inhibition of apoptosis," including cancers (such as follicular lymphomas), autoimmune disorders (such as rheumatoid arthritis) and graft versus host disease (GVHD). (Specification at page 38, lines 18-25.)

Based on the complete disclosure that Applicants have provided, one of ordinary skill in the art would understand that the claimed nucleic acids are useful in the diagnosis of diseases and/or disorders associated with aberrant cell survival, *e.g.*, cancers, and are useful in the diagnosis of diseases and/or disorders of the cells in which they are expressed, *e.g.*, lymphocytes. Accordingly, one of ordinary skill in the art would appreciate that the claimed nucleic acids are useful in the diagnosis of diseases associated with aberrant survival of lymphocytes including cancers such as follicular lymphomas, autoimmune disorders such as rheumatoid arthritis, and inflammatory disorders such as GVHD.

Applicants have included with this reply a Declaration Under 37 C.F.R. § 1.132 executed by Dr. Thi-Sau Migone [hereinafter "Declaration"]. This Declaration was originally filed in a corresponding sister application, U.S. Appl. No. 09/314,889, on November 7, 2002. Dr. Migone has studied DR3 and is the first named author of the publication entitled "TL1A Is a TNF-like Ligand for DR3 and TR6/DcR3 and Functions as a T Cell Costimulator," published in the peer-reviewed publication *Immunity* in March 2002. (Declaration, ¶ 3.)

In the Declaration, Dr. Migone states that her analysis of numerous experiments performed by herself or by other employees of the assignee indicates that DR3 is expressed at very low levels in normal resting T cells and at very low levels in normal B cells where it is sometimes undetectable. (Declaration, ¶ 21.) Furthermore, Dr. Migone states that Warzocha *et al.*, *Biochem. Biophys. Res. Comm.* 242:376-379 (1998) (previously submitted) shows that DR3 is "abundantly expressed" in a panel of pre-B acute lymphoblastic leukemia

cell lines as well as in each of eleven distinct clinical isolates of follicular lymphoma. (Declaration, ¶ 22.) Accordingly, Dr. Migone concludes, "Warzocha confirms that DR3 overexpression is useful as a diagnostic marker for certain lymphoid cancers such as acute lymphoblastic leukemia and follicular lymphoma." (*Id.*)

Dr. Migone further concludes that "[i]n light of the observed expression profile of DR3, together with the experimental results presented in the Warzocha paper, one of ordinary skill in the art would find it credible that DR3 is useful as a diagnostic marker for certain cancers, as disclosed in the Application." (Declaration, ¶ 24.)

Thus, the instant application provides an appropriate example of a situation "where an applicant discloses a specific biological activity and reasonably correlates that activity to a disease condition" and therefore provides a *specific* utility. (M.P.E.P. § 2107.01(I)[2100-32].) Additionally, this utility is *substantial*, since "[a]n assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease condition ... defines a 'real world' context of use." (MPEP § 2107.01(I) [2100-32].)

Based on the above, it is clear that the claimed invention satisfies the requirements of 35 U.S.C. § 101. The assertion that DR3 can be used in diagnostic applications to detect disclosed cancers is specific and substantial, and as stated by Dr. Migone, one of ordinary skill in the art would find such an assertion credible. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Having established at least one specific, substantial and credible utility for the invention, Applicants need not make any further showings in order to demonstrate that the claimed invention satisfies the requirements of 35 U.S.C. § 101. (*See, e.g.*, MPEP §

2107.02(I); *In re Gottlieb*, 328 F.2d 1016 (CCPA 1964) ("Having found that the antibiotic is useful for some purpose, it becomes unnecessary to decide whether it is in fact useful for the other purposes 'indicated' in the specification as possibly useful.")). Nonetheless, to clarify the record, Applicants make the following remarks.

1. The cellular responses to DR3 activation

In the previous reply, Applicants directed the Examiner to a reference authored by Dr. Migone: Migone *et al.*, *Immunity 16:*479-492 (2002). In the instant Office Action, the Examiner has alleged that "[t]his reference . . . clearly shows that the instant specification is fatally defective." (Paper No. 23, page 6.) For the following reasons, Applicants respectfully disagree.

The specification discloses that DR3 is a novel death domain-containing TNF receptor, which plays a role in cellular responses including apoptosis and cell proliferation. (*See e.g.*, Specification, page 1, lines 10-16; page 5, lines 15-20; page 6, lines 12-27; page 29, lines 9-16; page 39, lines 3-11; and page 41, lines 21-25.) As discussed below, this disclosure was credible to one of skill in the art at the time the application was filed, and it has been corroborated by post-filing evidence.

In the attached Declaration, Dr. Migone states that prior to the filing date of the present application, signaling through death domain-containing TNF receptor family members was known to cause both apoptosis and NF-κB activation, and that NF-κB activation is responsible for immune cell responses including proliferation. (Declaration, ¶¶ 9-10.) Dr. Migone concludes that the assertion that DR3 may induce apoptosis and proliferation "would have been credible to a scientist in the field of molecular biology." (Declaration, ¶ 11.)

Dr. Migone has further stated that the teachings of Migone *et al.* corroborate the disclosure of the specification with respect to DR3 function. Specifically, Dr. Migone has stated that "[i]n its totality, the Migone paper supports the disclosure of the Application and confirms that the effects of DR3 activation are context specific and that DR3 can act to promote apoptosis in certain cellular environments." (Declaration, ¶ 15; *See also*, Declaration, ¶¶ 8-11, and 14) Thus, contrary to what the Examiner believes, Dr. Migone has interpreted her own data as consistent with and confirmatory of Applicants' disclosure of DR3 function and activity.

2. Identification of the DR3 ligand, although not necessary to show utility, has subsequently confirmed Applicants' assertions of the cellular role of DR3.

The specification teaches that DR3 and/or agonists and antagonists thereof can be used to treat and/or diagnose cancers such as follicular lymphomas, inflammatory diseases such as Graft Versus Host Disease (GVHD), and autoimmune disorders such as rheumatoid arthritis. (*See e.g.*, Specification, page 6, lines 1-11; page 29, lines 9-17; page 38, lines 5-25; page 46, line 20 to page 47, line 3.) As discussed below, these assertions are credible even though the native ligand for DR3 had not yet been identified at the time of filing the instant application.

Migone *et al.* appear to have identified TL1A as the native ligand of DR3. Applicants submit that the identification of the native ligand of DR3 and subsequent studies involving DR3, while not necessary to establish utility of the instant application, serve to *confirm* the disclosure of the specification.

According to Dr. Migone, the Migone *et al.* publication confirms "that: (a) regulation of DR3 activation would modulate the physiological response believed to underlie inflammation and inflammatory diseases such as GVHD; (b) regulation of DR3 activation would regulate the unfettered cellular proliferation that is believed to underlie the development of certain cancers; and (c) regulation of DR3 activation would modulate development of immune responses which are necessary to control viral infections and which underlie autoimmune diseases such as rheumatoid arthritis." (Declaration, ¶ 26.)

Furthermore, as stated by Dr. Migone, Wang *et al.*, Mol. Cell. Biol. 21:3451-3461 (2001) provide further confirmation "that regulation of DR3 activation would modulate immune responses which underlie inflammation and inflammatory diseases such as GVHD, control of viral infections and certain autoimmune diseases such as rheumatoid arthritis." (Declaration, ¶ 28.) Thus, contrary to the Examiner's assertions, Wang *et al.* is relevant to Applicants' assertions.

3. The use of the claimed invention in generating agonistic antibodies against DR3 and DR3-V1 is a specific, substantial and credible utility.

In addition to a diagnostic utility, the specification asserts that the claimed invention can be used therapeutically. For example, the specification teaches that the claimed invention can, among other things, be used to generate agonists of DR3. *Such a utility does not require identification of a ligand.* An agonist is defined as an agent, e.g., an antibody, which is capable of increasing DR3 mediated signaling. (Specification, page 6, lines 1-5; page 39, lines 3-11.) Preferably, DR3 mediated signaling is increased to treat a disease wherein decreased apoptosis is exhibited. (*Id.* at page 39, lines 7-11.) According to the specification,

specific diseases which exhibit decreased apoptosis include cancers such as follicular lymphoma, autoimmune diseases such as rheumatoid arthritis, viral infections and inflammatory diseases such as GVHD. (*See, e.g.*, page 38, lines 18-21.)

At the time of filing, it was recognized in the art that agonistic antibodies against TNF receptor family members could be used to trigger receptor mediated signaling. For example, Tartaglia & Goeddel, *J. Biol. Chem.* 267: 4304-4307 (1992) (already submitted) demonstrate the use of agonistic antibodies to trigger signaling mediated by TNF-R1, another death domain-containing TNF receptor family member. Indeed, Tartaglia & Goeddel state that "[b]oth polyclonal and monoclonal antibodies directed against human TNF-R1 have been shown to behave as receptor agonists." (Tartaglia & Goeddel at 4304, column 2 (citations removed)). In their own experiments, Tartaglia & Goeddel show that the 55-kDa TNF receptor, stably expressed in mouse L929 cells, was activated specifically by agonist antibodies. (*Id.* at column 1.)

Other studies have shown that agonistic antibodies against TRAIL-R1, another death domain-containing TNF receptor family member, have anti-tumor effects *in vitro* and *in vivo*. For example, Salcedo *et al.*, in a poster which was presented at the 93rd Annual Meeting of the American Association for Cancer Research (AACR) held in San Francisco, California on April 6-10, 2002 (an enlarged copy of which is attached as Exhibit 1), found that TRM-1, a human agonistic antibody specific for TRAIL-R1, induced apoptosis in human cancer cell lines *in vitro* and reduced tumor growth in human colon and uterine xenograft models in nude mice. (*See*, Conclusions, columns 5-6.) In addition, TRM-2, a human agonistic antibody specific for TRAIL-R2 (another death domain-containing TNF receptor family member), was found to be effective in reducing or preventing tumor growth in human colon xenograft models in nude mice. (*Id.*)

Applicants submit that the teachings of Tartaglia & Goeddel and Salcedo *et al.* corroborate the assertion that agonists (e.g., antibodies) against DR3 could specifically trigger receptor signaling in the absence of a known receptor ligand. Furthermore, Dr. Migone has stated that Migone *et al.* and Wang *et al.* "together and individually, provide credible and compelling support" for the use of DR3 in the treatment of "diseases such as cancers, including follicular lymphomas; inflammatory diseases, including Graft Versus Host Disease (GVHD); viral infections; and certain autoimmune disease such as rheumatoid arthritis." (Declaration, ¶ 29.)

In view of the above remarks it is clear that at least one assertion concerning utility of the invention is specific, substantial and credible. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the pending claims under 35 U.S.C. § 101.

V. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has maintained his rejection of claims 27-75 under 35 U.S.C. § 112, first paragraph. (Paper No. 23, page 7.) The Examiner contends that since the claimed invention is not supported by either a credible, substantial and specific asserted utility or a well-established utility, for the reasons above with regards to the rejection under 35 U.S.C. § 101, one skilled in the art would not know how to use the claimed invention. As claims 47-75 have been canceled, Applicants respectfully traverse the rejection as it applies to the pending claims.

In view of the above, the claimed invention has a patentable utility under 35 U.S.C. § 101. The Examiner "should not impose a 35 U.S.C. § 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. § 101 rejection is proper." (M.P.E.P. § 2107(IV) at 2100-28.) Therefore, since the claimed invention complies with the utility requirement of 35 U.S.C. § 101, the rejection of claims under 35 U.S.C. § 112, first paragraph, based on lack of utility of the claimed invention, should be withdrawn.

VI. Claim Rejections Under 35 U.S.C. § 102(b)

The Examiner has rejected claims 27–46 under 35 U.S.C. § 102(b) as allegedly being anticipated by each of Chinnaiayn *et al.*, *Science* 274: 990-92 (1996) and Kitson *et al.*, *Nature* 384:372-375 (1996). (Paper No. 23, page 7.) The Examiner contends that the cited references are available as prior art because the priority applications of the present case are unavailable under 35 U.S.C. § 120. The Examiners' rationale is that because the present application does not meet the requirements of 35 U.S.C. § 112, first paragraph, the prior applications also do not meet this requirement. Applicants respectfully traverse this rejection.

As discussed above, Applicants believe that the requirements of 35 U.S.C. § 112, first paragraph, have been satisfied for the present application. The requirements of 35 U.S.C. § 112, first paragraph, have also been satisfied for the earlier priority applications. Accordingly, Applicants submit that neither Chinnaiayn *et al.* nor Kitson *et al.* is available as prior art. Reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Eric K. Steffe
Attorney for Applicants
Registration No. 36,688

Date: 11/21/02

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

In the Claims:

Claims 47-75 are sought to be canceled.